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Studying co-medication patterns: The impact of definitions

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Abstract

Objectives

To show the necessity of distinguishing several patterns of drug prescribing that may lead to co-medication. It is demonstrated how these different patterns can be investigated using large databases containing pharmacy data or reimbursement data.

Methods

Two examples illustrate how the particular pattern of co-medication studied influence the reported proportion of patients having co-medication; the use of antidepressants among people using anti-epileptics, and the use of antihistamines among people receiving penicillines

Results

Depending on definition and period considered, the percentage of anti-epileptic users co-medicated with anti-depressants ranged from 5.8% (95% CI 5.0%, 6.8%) to 14.5% (95% CI 13.2%, 15.9%) in 2000. Comparing 2002 with 2000, the ratio of proportions ranged from 1.3 to 2.1. The percentage of people who received penicillines and were co-medicated with antihistamines ranged from 0.5% (95% CI 0.4%, 0.6%) to 9.7 (95% CI 9.3%, 10.2%) in 2000. Comparing 2002 with 2000, the ratio of proportions ranged from 1.2 to 1.6.

Conclusions

The co-medication patterns investigated yielded clinical as well as statistical significant different estimates. The estimates differed up to a factor 2.5 for the drugs usually prescribed for long periods, and a factor 12 for drugs prescribed for short periods. Hence, we propose to distinguish the patterns 'co-prescribing', 'concomitant medication' and 'possibly concurrent medication'. The research question determines the co-medication pattern of interest, and the drug and disease under study determine the time window

Introduction

The use of two or more drugs is a general concern since efficacy and safety of most drugs are investigated for single use alone. Co-medication has also become an important concept in the context of prescribing quality markers [1]. A variety of terms is used to refer to the use of two or more drugs within the same time frame; co-medication, concomitant medication, concurrent medication, co-administration and multiple pharmacotherapy. Medline and Embase thesauruses include ‘drug combinations’, single preparations containing two or more drugs as a fixed dose, and ‘drug therapy, combination’, two or more drugs administered separately for a combined effect, both terms implying intended use of two or more drugs together. Since no entry refers to the use of two drugs regardless of whether they are part of the same treatment, this variety of terms seems inevitable. This labyrinth of terminology causes problems for systematic reviews and meta-analyses as well as the search for knowledge on particular combinations of drug classes in daily clinical practice. For example, in a review on concomitant psychotropic drug use in children and teenagers, definitions ranged from more than two psychotropic drugs being prescribed by the same doctor on the same day to the same patient to children who received within the same year prescriptions for two or more psychotropic drugs regardless of prescriber, which lead to a variety of poorly comparable estimates [2]. And a review on gender differences in the prescribing of antipsychotic drugs referred to patterns of co-medication with concurrent medication, adjunct drugs, concomitant drugs and co-administered drugs without any explicit definition but implying the purposefully prescribing of two or more drugs to the same patient allowing for different prescribers [3].

Consensus is called for to be able to communicate results unambiguously to clinicians and researchers. For the sake of clarity let us define co-medication as the most general term that covers the actual taking of two prescription drugs on the same day, regardless of the prescribers’ intentions. Then, since not all patterns of co-medication may be of equal interest and not all patterns lead to the same estimates of proportion of patients involved, several possible co-medication patterns ought to be distinguished. We aim to demonstrate the necessity of distinguishing several patterns of drug prescribing that may lead to co-medication, by illustrating the impact of different co-medication patterns on the proportion of patients having had co-medication in a large pharmacy database.

Methods

Definitions

Several patterns of co-medication can be defined. With the prefix ‘co-‘in the meaning of jointly [4], ‘co-prescribing’ is defined as ‘the jointly prescribing of more than one drug by the same prescriber on the same day’. As concomitant means concurrent [4], ’concomitant medication’ is defined as the concurrent use of drugs as prescribed by one or more different medical doctors not necessarily on the same day. Co-prescribing and concomitant medication cover co-medication resulting from the use of drugs as intended by medical doctors. Of course, co-medication may also result from two drugs simply being available to the patient because they have been dispensed within a certain time period and some left over pills may still be left in the medicine cabinet. This latter source of co-medication is classified as “possibly concurrent”.

Table 1. Classification of co-medication patterns.

		Criteria		
Pattern	Co-medication	Same prescriber	Overlap	Time between prescriptions
Co-prescribing	Intentional	Y	Y	Same day
Concomitant	Likely	-	Y	Same day
		-	Y	± 7 days
		-	Y	± 15 days
		-	Y	± 30 days
Possibly concurrent	Possibly	-	-	Same month
		-	-	Quartile
		-	-	Halve year
		-	-	Year

Definitions made operational

Prescriptions were identified as co-prescribed if written by the same doctor on the same day to the same patient (Table 1). Concomitant medication was made operational as drugs dispensed within a certain time period while according to information available in the pharmacy computer system, the two prescriptions overlap in time. The duration of any prescription is derived by dividing the quantity dispensed by the daily dose prescribed as registered in the pharmacy. The following time windows were chosen; same day, +/- seven days, +/- 15 days and +/- 30 days. Note that ‘concomitant medication’ allows for different prescribers. Operationally, concurrent medication is two or more drugs under study dispensed within a certain time period regardless of overlap between prescriptions. Hence, possibly concurrent medication is identical to (calendar) period prevalence of a drug among the users of another drug. Periods investigated were month, quartile, halve a year and year.

Note that both 'concomitant +/- 15 days' dispensed and 'possibly concurrent – month prevalence' have a similar study length of 30 or 31 days.

Data selection

As a source of pharmacy data The InterAction DataBase is used [5]. The InterAction DataBase is part of the collaboration between community pharmacists in the northern and eastern part of the Netherlands and the department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy at the University of Groningen, and comprises all prescriptions dispensed by community pharmacies regardless of reimbursement status, from 1994 up to now, and covers anonymized prescriptions for about 450,000 people since 1999.

As a first index drug anticonvulsants of the ATC category N03A entitled antiepileptics were chosen [6] As possible co-medication the drug group antidepressants (ATC category N06A) was chosen, as this combination received a lot of attention lately, mainly in the context of the treatment of bipolar disorder [7,8]. Also, both drugs are usually intended for a longer period of treatment whereas the second example concerns drugs that are intended for a shorter period of use. The second index drug class was penicillines (ATC category J01C) with antihistamines (ATC category R06A) as co-medication.

In the first example, the study group consisted of people between five and 54 years of age who received at least one anticonvulsant prescription in 2000. For members of the study group all prescriptions of anticonvulsants and antidepressants dispensed in the year 2000 were selected. To study concomitant medication with a time window of one month, antidepressant prescriptions dispensed in December 1999 and January 2001 were also selected. Similarly, a study group with prescriptions was retrieved for the year 2002. Since the patient is the level of interest in the issue of co-medication, person is the unit of analysis. Thus all prescription data were aggregated at the person-level. In the second example, the study group consisted of people in the same age range who received at least one prescription for penicillines. Then, all prescriptions of penicillines and antihistamines for the members of this study group were selected as described above.

For all patterns of co-medication, the percentage of people with co-medication was calculated as the number of people who once or more fit the particular co-medication pattern divided by the number of people having received anticonvulsants (or penicillines) that same year. 95% confidence intervals (CIs) were calculated using the 'Pearson-Clopper' Exact method' [9]. To investigate the differences in trend for the co-medication patterns from one year to an other year, the ratio of the proportions for two years (the relative prevalence) is also calculated.

Results

In the year 2000, 2701 people had received at least one prescription for anticonvulsants. In 2002, unto 2995 people anticonvulsants were dispensed. Depending on definition and period considered, the percentage of anticonvulsant users co-medicated with an antidepressant ranged from 6% to 14% in 2000. In 2002, these ranged from 10% to 18% (Table 2). The relative prevalence (%2002/%2000) ranged from 1.2 to 1.9.
Table 3 shows the percentages of the more than 27 000 people who received at least one prescription for penicillines and were co-medicated with antihistamines. The entries in this table are smaller than those in table 2, reflecting the difference between drugs usually prescribed for a longer period versus ones prescribed for shorter courses. Depending on definition and period considered, the percentage of penicillines users co-medicated with an antidepressant ranged from 0.5% to 9.7% in 2000. These percentages ranged from 0.9% to 11.2% in 2002. The relative prevalence ranged from 1.2 to 1.6.

In general, prevalence of co-medication increased with time period considered. The difference between co-prescribing and concomitant same day could be clinically relevant but there is no statistical reason to differentiate between these two estimates in the presented examples (Table 2 and Table 3). One would have expected the additional demand of overlap for classification as concomitant to result in smaller estimates than possibly concurrent. For the penicillines and antihistamines example, this expectation came true; concomitant +/- 15 days and possibly concurrent one month yielded statistically significant estimates. However, this was not the case for the anticonvulsants and antidepressants; concomitant +/- 15 days and possibly concurrent one month yielded no statistically significant different results. The different patterns did not only yield significant differences on the percentage scale but also on the ratio scale as for both examples the range in relative prevalence is considerable.

Discussion

We illustrated how different definitions may lead to both clinically and statistically significant different proportions of people being co-medicated. The impact is also evident when looking at the relative prevalence of co-medication patterns. Whether or not our results are limited to

Table 2. Percentage of patients receiving anticonvulsants in 2000 (n = 2701) and 2002 (n = 2995) co-medicated with antidepressants according to the definitions and time windows described and the ratio between the percentages in these two years.

		2000			2002			Ratio scale
Pattern	Period	N	%	95% CI	N	%	95% CI	% 2002 /%2000
Co-prescribing	Same day	158	5.85	4.99 – 6.80	312	10.42	9.35 – 11.57	1.78
Concomitant	Same day	166	6.15	5.27 – 7.12	327	10.92	9.82 – 12.09	1.78
	+/- 7 days	179	6.63	5.72 – 7.63	370	12.35	11.20 – 13.59	1.86
	+/- 15 days	216	8.00	7.00 – 9.08	406	13.56	12.35 – 14.83	1.70
	+/- 30 days	267	9.89	8.79 – 11.07	435	14.52	13.28 – 15.84	1.47
Possibly concurrent	Month	226	8.37	7.35 – 9.48	411	13.72	12.51 – 15.00	1.64
	Quartile	282	10.44	9.31 – 11.66	469	15.66	14.38 – 17.01	1.50
	Halve year	349	12.92	11.68 – 4.24	503	16.79	15.47 – 18.18	1.30
	Year	391	14.48	13.17 – 15.86	531	17.73	16.38 – 19.15	1.22
Total anticonvulsants users		2701			2995	100.0		

Table 3. Percentage of patients receiving penicillines in 2000 (n = 27149) and 2002 (n = 27278) co-medicated with antihistamines according to the definitions and time windows described and the ratio between the percentages in these two years.

		2000			2002			Ratio scale
Pattern	Period	N	%	95% CI	N	%	95% CI	% 2002 /%2000
Co-prescribing	Same day	143	0.53	0.44 – 0.62	236	0.87	0.76 – 0.98	1.64
Concomitant	Same day	157	0.58	0.49 – 0.68	260	0.95	0.84 – 1.08	1.65
	+/- 7 days	407	1.50	1.36 – 1.65	606	2.22	2.05 – 2.40	1.48
	+/- 15 days	504	1.86	1.70 – 2.02	750	2.75	2.56 – 2.95	1.48
	+/- 30 days	589	2.17	2.00 – 2.35	870	3.19	2.98 – 3.40	1.47
Possibly concurrent	Month	630	2.32	2.14 – 2.51	938	3.44	3.23 – 3.66	1.48
	Quartile	1137	4.19	3.95 – 4.43	1616	5.92	5.65 – 6.21	1.41
	Halve year	1827	6.73	6.43 – 7.03	2231	8.18	7.86 – 8.51	1.22
	Year	2622	9.66	9.31 – 10.2	3060	11.22	10.85 – 11.60	1.16
Total penicillin users		27149	100.0		27278	100.0		

database research, they have huge consequences for research. Only after scrutinizing definitions and time-windows it is valid to make comparative statements like “co-medication with antidepressants is less prevalent in the current study than in the literature” or “co-medication with antihistamines has increased since the seventies”.

In the two examples in this paper the point estimates differed a factor 2.5 (from 5.8% to 14.5%) for the percentage of people receiving anticonvulsants who were being co-medicated with anti-depressants. The point estimates were smaller for the proportion of people receiving penicillines who were co-medicated with antihistamines, and these estimates differed up to a factor 12 (from 0.5% to 9.7%). The relative prevalence (%2002/%2000) also showed a clinically significant range from 1.2 to 1.9 for the anticonvulsants with antidepressants, and 1.2 to 1.6 for the penicillines with antihistamines.

The completeness of medication dispensing data is essential for the study of co-medication patterns. The advantage of pharmacy dispensing data over claims data is that often all prescription medication is included regardless of reimbursement status of the particular drug. Pharmacy data will also be more complete on prescription medication than the GPs or specialist’s files. However, in contrast to these, no information on switching medication is available in either pharmacy data or claims data. Especially in the study of co-medication with two drugs from the same class, this may be a problem as switching may be miss-classified as co-medication and the other way around [10].

Co-medication in the meaning of Medline’s thesaurus’ ‘drug therapy, combination’, where two or more drugs are administered separately for a combined effect, demands the information on indication. Since reliable information on indication is available in neither pharmacy data nor claims data, ‘drug therapy, combination’ can not be studied when depending on these data sources alone. However, these data sources are very suitable for study of ‘drug combinations’, meaning single preparations containing two or more active agents as a fixed dose (see Medline’s thesaurus).

No previous study to our knowledge has investigated co-medication like the present study did, by means of examples of only hypothetical interest. Other studies were initiated because of their interest in co-medication of two or more specific drugs. Few studies went beyond the mere presenting of one proportion and showed large differences in point estimates of co-medication due to differences in time window. One study on pharmacotherapy among youths enrolled in Medicaid reported 13.6% of the children receiving at least two different classes of psychotropic drugs within a one-week interval, and 42% of the children when a three-month window was used instead [11]. A study on youths treated with stimulants that relied on pharmacy dispensing data, reported 15% of children

being co-medicated with another psychotropic agent when using a one-week interval and 21% when a one year prevalence was used [12].

Since co-medication is of general interest and the variety of terminology in use obstruct the clear communication between clinicians and researchers, we propose a first step towards unambiguous terminology. We suggest to use co-prescribing for the study of prescribing quality markers. Concomitant medication would be reserved for the study of increased use of drug-drug combinations not investigated together for safety and efficacy, as in this case both sensitivity and specificity are of importance. Possibly concurrent medication is most suitable when high sensitivity is demanded for, as is the case for the study of evident safety concerns. Clearly, the drugs of interest, the underlying ailments being treated, and possible safety aspects are important to consider when deciding on the time window.

References

1. Schubert I, Ihle P, Köster I, von Ferber L. Markers to analyse the prescribing of non-steroidal anti-inflammatory drugs in ambulatory care. Eur J Clin Pharmacol 1999;55:479-486
2. Safer DJ, Zito JM, dosReis S. Concomitant psychotropic medication for youths. Am J Psychiatry 2003;160:438-449
3. Seeman MV. Gender differences in the prescribing of antipsychotic drugs. Am J Psychiatry 2004;161:1324-1333
4. Oxford English Dictionary. Oxford University Press [2nd Ed. 1989]. Accessed June 28, 2005 (http://dictionary.oed.com)
5. Tobi H, van den Berg PB, de Jong-van den Berg LTW. The InterAction database: synergy of science and practice in pharmacy. Lect Notes Comput Sc 2000; 1933:206-211
6. WHO Collaborating Centre for Drugs Statistics Methodology. Accessed April 19, 2005 (http://www.whocc.no/atcddd/)
7. Gijsman HJ, Geddes JR, Rendell JM, Nolen WM, Goodwin GM. Antidepressants for Bipolar Depression: A Systematic Review of Randomized, Controlled Trials. Am J Psychiatry 2004; 161:1537-1547
8. Silverstone PH, Silverstone T. A review of acute treatments for bipolar depression. Int J Clin Psychopharmacol 2004;19:113-124
9. Tobi H, van den Berg PB, de Jong-van den Berg LTW. Small proportions: What to report for confidence intervals? Pharmacoepidemiol Drug Saf 2005;14:239-427
10. Leslie DL, Rosenheck RA. Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system. Med Care 2001;39:923-933
11. Martin A, van Hoof T, Stubbe D, Sherwin T, Scahill L. Multiple psychotropic pharmacotherapy among children and adolescent enrollees in Connecticut medicaid managed care. Psychiatric Services 2003;53:72-77

12. Faber A, de Jong-van den Berg LTW, van den Berg PB, Tobi H. Psychotropic co-medication among stimulant-treated children in the Netherlands. J Child Adolesc Psychopharmacol 2005;15:38-43